THE ROLE OF INTRAVITREAL BEVACIZUMAB IN THE MANAGEMENT OF VARIOUS RETINAL VASCULAR DISEASES

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Proforma

Master Chart

Introduction

INTRODUCTION

ANGIOGENESIS

Angiogenesis is a physiological process involving the growth of new blood vessels from pre existing vessels. Though there has been some debate over this, vasculogenesis is the term used for spontaneous blood-vessel formation, and intussusception is the term for new blood vessel formation by splitting off existing ones.

Types

Sprouting angiogenesis

Sprouting angiogenesis was the first identified form of angiogenesis. It occurs in several well characterized stages. First, biological signals known as angiogenic growth factors activate receptors present on endothelial cells present in pre-existing veins. Second, the activated endothelial cells begin to release enzymes called proteases that degrade the basement membrane in order to allow endothelial cells to escape trom the original (parent) vessel walls. The endothelial cells then proliferate into the surrounding matrix and form solid sprouts connecting neighboring vessels. As sprouts extend toward the source of the angiogenic stimulus, endothelial cells migrate in tandem, using adhesion molecules, the equivalent of cellular grappling hooks, called integrins. These sprouts then form loops to become a full-fledged vessel lumen as cells migrate to the site of angiogenesis. Sprouting occurs at a rate of several millimeters per day, and enables new vessels to grow across gaps in the vasculature. It is markedly different from splitting angiogenesis, however, because it forms entirely new vessels as opposed to splitting existing vessels.

Intussusceptive angiogenesis

Intussusception, also known as splitting angiogenesis, was first observed in neonatal rats. In this type of vessel formation, the capillary wall extends into the lumen to split a single vessel in two. There are four phases of intussusceptive angiogenesis. First, the two opposing capillary walls establish a zone of contact. Second, the endothelial cell junctions are reorganized and the vessel bilayer is perforated to allow growth factors and cells to penetrate into the lumen. Third, a core is formed between the two new vessels at the zone of contact that is filled with pericytes and myofibroblasts. These cells begin laying collagen fibers into the core to provide an extracellular matrix for growth of the vessel lumen. Finally, the core is fleshed out with no alterations to the basic structure. Intussusception is important because it is a reorganization of existing cells. It allows a vast increase in the number of capillaries without a corresponding increase in the number of endothelial cells. This is especially important in embryonic development, as there are not enough resources to create a rich microvasculature with new cells every time a new vessel develops.

Modern terminology of angiogenesis

Besides the differentiation between "Sprouting angiogenesis" and "Intussusceptive angiogenesis" there exists the today more common differentiation between the following types of angiogenesis.

Vasculogenesis - Formation of vascular structures from circulating or tissue-resident endothelial stem cells (angioblasts), which proliferate into de novo

endothelial cells. This form particularly relates to the embryonal development of the vascular system.

Angiogenesis - Formation of thin - walled endothelium-lined structures with/without muscular smooth muscle wall and pericytes (fibrocytes). This form plays an important role during adult life span, also as "repair mechanism" of damaged tissues.

Arteriogenesis - formation of medium - sized blood vessels possessing tunica media plus adventitia

Because it turned out even this differentiation is not a sharp one, today quite often the term "Angiogenesis" is used summarizing all different types and modifications of artierial vessel growth.

ANGIOGENESIS PROTEINS

Stimulator	**Mechanism**
FGF	Promotes proliferation & differentiation of endothelial cells , smooth muscle cells and fibroblasts
VEGF	Affects permeability
VEGFR and NRP-1	Integrate survival signals
Angl and Tie2	Stabilize vessels
PDGF(BB-Homodimer) and PDGFR	Recruit smooth muscle cells
TGF-β,endoglin and TGF –β receptors	↑ extracellular matrix production
MCP-1	
Integrins αvβ3, αvβ5(?[9]) and α5β1	Bind matrix macromolecules and proteinases
VE-Catherin andCD31	Endothelial junctional molecules
Ephrin	Determine formation of arteries vein
Plasminogen activators	Remodels extra cellular matrix release and activates growth Factors
Plasminogen activator inhibitor-1	Stabilize nearby vessels
NOS and COX-2	
AC133	Regulate angioblast differentiation
1d1 / 1d3	Regulates endothelial trans differentiation

FGF (Fibroblast Growth Factor)

The fibroblast growth factor (FGF) family with its prototype members FGF - 1 (acidic FGF) and FGF - 2 (basic FGF) consists to date of at least 22 known members. Most are 16-18 kDa single chain peptides and display high affinity to heparin and heparin sulfate. In general, FGFs stimulate a variety of cellular, functions by binding to cell surface FGF - receptors in the presence of heparin proteoglycans. The FGF - receptor family is composed of seven members and all the receptor proteins are single chain receptor tyrosine kinases that become activated through autophosphorylation induced by a mechanism of FGF mediated receptor dimerization. Receptor activation gives rise to a single transudation cascade that leads to gene activation and diverse biological responses, including cell differentiation, proliferation, and matrix, dissolution - thus initiating a process of mitogenic activity critical for the growth of endothelial cells, fibroblasts, and smooth muscle cells. FGF -1, unique among all 22 members of the FGF family, can bind to all seven FGF - receptor subitypes, making it the broadest acting member of the FGF family, and a potent mitogen for the diverse cell types needed to mount an angiogenic response in damaged (hypoxic) tissues, where up regulation of FGF - receptors occurs. FGF- I stimulates the proliferation and differentiation of all cell types necessary for building an arterial vessel, including endothelial cells and smooth muscle cells, this fact distinguishes FGF -1 from other proangiogenic growth factors, such as vascular endothelial growth factor (VEGF) which primarily drives the formation of new capillaries.

Until now (2007), three human clinical trials have been successfully completed with FGF -I in which the angiogenic protein was injected directly into the damaged heart muscle. Also, one additional human FGF-I trial has been completed to promote wound healing in diabetics with chronic wounds.

Besides FGF-I, one of the most important functions of also fibroblast growth factor-2 (FGF-2 or bFGF) is the promotion of endothelial cell proliferation and the physical organization of endothelial cells into tube-like structures, thus promoting angiogenesis. FGF-2 is a more potent angiogenic factor than VEGF or PDGF (platelet-derived growth factor), however, less potent than FGF-l. As well as stimulating blood vessel growth, a FGF (FGF-I) and Bfgf (FGF-2) are important players in wound healing. They stimulate the proliferation of fibroblasts and endothelial cells that give rise to angiogenesis and developing granulation tissue, both increase blood supply and fill up a wound space/cavity early in the wound healing process.

VEGF (Vascular Endothelial Growth Factor)

VEGF (Vascular Endothelial Growth Factor) has been demonstrated to be a major contributor to angiogenesis, increasing the number of capillaries in a given network. Initial in Vitro studies demonstrated that bovine capillary endothelial cells will proliferate and show signs of tube structures upon stimulation by VEGF and b FGF, although the result were more pronounced with VEGF. Upregulation of VEGF is a major component of the physiological response to exercise and its

role in angiogenesis is suspected to be a possible treatment in vascular injuries.

In vitro studies clearly demonstrate that VEGF is a potent stimulator of angiogenesis because in the presence of this growth factor plated endothelial cells will proliferate and migrate, eventually forming tube structures resembling capillaries. VEGF causes a massive signaling cascade in endothelial cells. Binding to VEGF receptor -2 (VEGFR-2) starts a tyrosine kinase signaling cascade that stimulates the production of factors that variously stimulate vessel permeability (eNoS, producing NO), proliferation/survival (Bfgf), migration (ICAMSNCAMs/MMPs) and finally differentiation into mature blood vessels. Mechanically, VEGF is upregulated with muscle contractions as a result of increased blood flow to affected areas. The increased flow also causes a large increase in the m RNA production of VEGF receptors 1 and 2. The increase in receptor production means that muscle contractions could cause upregulation of the signaling cascade relating to angiogenesis. As part of the angiogenic signaling cascade, NO is widely considered to be a major contributor to the angiogenic response because inhibition of NO significantly reduces the effects of angiogenic growth factors. However, inhibition of NO during exercise does not inhibit angiogenesis indicating that there are other factors involved in the angiogenic response.

Angiopoietins

The angiopoietins, Angl and Ang2, are required for the formation of mature blood vessels, as demonstrated by mouse knock out studies. Angl I and Ang 2 are protein growth factors which act by binding their receptors. Tie-l and Tie-2, while

this is somewhat controversial, it seems that cell signals are transmitted mostly by Tie-2, though some papers show physiologic signaling via Tie-l as well. These receptors are tyrosine kinases. Thus, they can initiate cell signaling when ligand binding causes a dimerization that initiates phosphorlation on key tyrosines.

MATRIX METALLO PROTEINASE

Another major contributor to angiogenesis is matrix metallo proteinase (MMP). MMPs help degrade the proteins that keep the vessel walls solid. This proteolysis allows the endothelial cells to escape into the interstitial matrix as seen in sprouting angiogenesis. Inhibition of MMPs prevents the formation of new capillaries. These enzymes are highly regulated during the vessel formation process because destruction of the extracellular matrix would decrease the integrity of the microvasculature.

Aim of the Study

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To evaluate the safety and efficacy of intravitreal Bevacizumab in the management of various retinal vascular diseases.

Review of Literature

REVIEW OF LITERATURE

Many retinal diseases occur due to abnormal angiogencsis, these include vascular disorders such as Diabetic Retinopathy, Vein Occlusions and Age related Macular Degeneration.

A) DIABETIC RETINOPATHY

Diabetic retinopathy is a leading cause of severe loss of visual acuity in developed countries. About 25 % of diabetic patients have sight threatening levels of retinopathy with legal blindness.

ETIOPATHOGENESIS

The exact cause of diabetic microvascular disease is unknown. It is believed that exposure to hyperglycemia over extended period results in a number of biochemical and physiologic changes that ultimately cause vascular endothelial damage.

Pathogenesis of Microvascular occlusion

1. Basement membrane thickening
2. Damage and proliferation of endothelial cells
3. Increased erythrocyte aggregation leading to defective oxygen transport.
4. Increased platelet adhesiveness
5. Abnormal levels of growth hormones such as Vaso Endothelial Growth Factor
6. Defective fibrinolysis
7. Abnormal serum lipids
8. Increased blood viscosity

Pathogensis of Microvascular Leakage (Jack J. Kanski, 5th Edition, p.no 440)

1. Breakdown of inner blood retinal barrier (i.e tight junctions of capillary endothelium)
2. Loss of pericytes leads to physical weakening of capillary wall resulting in localized vascular outpouchings termed micro aneurysms which may leak or become thrombosed

SIMPLE BACKGROUND DIABETIC RETINOPATHY

CLINICAL FEATURES

1. Microaneurysms
2. Intraretinal haemorrhages
3. Hard exudates
4. Retinal oedema

MANAGEMENT

Eyes with simple background Diabetic Retinopathy not associated with clinically significant macular oedema do not require laser treatment.

CLINICAL FEATURES OF DIABETIC MACULAR EDEMA

It is the most common cause of visual impairment in diabetic patients, particularly those with type II diabetes.

Focal Exudative

Signs: Well circumscribed retinal thickening associated with complete or incomplete rings of hard exudates derived from plasma lipoprotein that appears to emanate from microaneurysms.

Fundus Fluorescein Angiography (FFA): Shows late focal hyperfluorescence due

to leakage and good macular perfusion.

Diffuse Exudative

Signs: Diffuse retinal thickening, which may be associated with cystoid changes.

FFA: Shows widespread spotty hyperfluorescence of micro aneurysm and late diffuse hyperfluorescence due to leakage. Flower petal pattern is seen in case of cystoid macular edema.

Ischemic

Signs: Reduced visual acuity with a relatively normal appearance of fovea. Dark blot hemorrhages may be seen.

FFA: Shows capillary non perfusion at the fovea and enlargement and irregularity of foveal avascular zone (FAZ)

Mixed

Signs: Characterized by features of both ischemic and exudative.

Chinical Significant Macular Edema (CSME)

ETDRS defined clinically significant macular edema as anyone of the following.

I. Retinal edema located at or within 500μ of the center of the macula.
II. Hard exudates at or within 500μ of the center of associated with thickening of adjacent retina.
III. A zone of retinal thickening larger than 1 disc area if located within 1 disc diameter of the centre of the macula.

CSME requires laser photocoagulation irrespective of the level of visual acuity because treatment reduces the risk of visual loss by 50%.

Adamis et al., have studied that features of chronic inflammation such as adhesion

of leucocytes to the retinal vasculature and migration into retina, may playa role in diabetic maculopathy and retinopathy.

Preproliferative diabetic retinopathy

CLINICAL FEATURES

1. Vascular changes
2. Cotton - wool spots
3. Dark blot haemorrhages
4. lntraretinal microvascular abnormalities

MANAGEMENT

Patients with preprolifertative changes should be watched closely because a significant number develop proliferative Diabetic Retinopathy. Treatment by photocoagulation is usually unnecessary unless regular follow - up is impossible, especially if the patient has lost sight in the fellow eye from complications of proliferative Diabetic Retinopathy.

Proliferative diabetic retinopathy

CINICAL FEATURES

1. Neovascularization
2. Vitreous detachment
3. Haemorrhage

INDICATIONS FOR TREATMENT

The indication for treatment depends on the risk of subsequent severe visual loss.

The following are the clinical features of eyes at high risk:

a) NVD or neovascularization within one disc diameter of the optic disc more than one quarter disc in area.

b) Less extensive NVD, if associated with vitreous or preretinal haemorrhage.

c) NVE more than one - half disc in area if associated with vitreous or preretinal haemorrhage.

B. RETINAL VEIN OCCLUSIVE DISEASE

RETINAL VEIN OCCLUSIVE DISEASE

Predisposing Factors

Common

1. Advancing Age
2. HTN
3. Hyperlipidemia
4. Diabetes mellitus
5. Raised IOP

Uncommon

1. Myeproliferative Disorders
2. Acquired Hypercoaguable states
3. Inherited Hyper coaguable states
4. Inflammatory disease associated with Occulusive periphletitis

Pathogenesis

Athersclerosis (BRVO)

↓

Retinal arteriole & vein share

↓

Common adventitious sheath

↓

Thickening of sheath

↓

Compres the vein

↓

2^0 Changes

- Vein endothelial loss
- Thrombus formation
- Occlusion

BRANCH RETINAL VEIN OCCLUSION

CLASSIFICATION

1. Major BRVO

- First Order Temporal Branch at the optic Disc
- First Order Temp Branch away from the Disc but involving the branches to the Macula.

2. Minor Macular BRVO

- Involving only a Macular Branch

3. Peripheral BRVO

- Not involving the Macular circulation

Diagnosis

1. Presentation → Sudden Onset of Blurred Vision and Metamorphopsia or a relative Visual field defect.
2. Visual Activity is Variable
3. Fundus → Dilatation and Tortusity of Veins distal to the site of Occlusion and attenuation/Flame shaped, and Dot & Blot Hge, retinal oedema & cotton wool spot.
4. FA → Shows delayed Vein filling, hyperfluoroscene due to leakage, hypofluoroscence due to Capillary non – perfusion.
5. Course → Acute Features (6-12 Months)

- Hard Exudates, Vein Sheathing and sclerosis peripheral to the site of Obstruction

- Collateral Vein channels between the superior & Inferior vascular Arcades

Prognosis

- The two main Vision threatening Complications are

  i) Chronic Macular oedema

  ii) Neovascularization ---- NVD - 10 %
  NVE - 25 %

Follow Up → is within 6 – 12 Weeks within FA

Further treatment depends on Visual Acuity and angiographic findings as follows

- Good macular perfusion and Visual Acuity is improving, No Treatment
- Macular oedema is asstd with good macular Perfusion and Visual Acuity Continues to be 6/12 or, worse Laser Photocoagulation should be Considered
- If FA shows Foveal Avascular Zone is broken, laser is less likely to improve Visual Acuity Macular Non Perfusion and Visual Acuity is Poor, Laser treatment will not improve Vision

Treatment

1. Macular Ocdema

   a) Grid Laser Photocoagulation 100 -200 µ

      0.1 Sec

   b) Intra Vitreal Avastin may improve Visual Acuity

2. Neovascularization is normally treated unless Vitreous Hge Occurs

Laser Photocoagulation 200 – 300 µ

0.5 – 0.1 Sec

A quadrant usually requires 400 - 500 burns

Follow up Should be after 4 – 6 Weeks

Non ISCHAEMIC Central Retinal Vein Occlusion

Non ISCHAEMIC Central Retinal Vein Occlusion accounting 75% of all cases.

Diagnosis

- Sudden U/L Blurred Vision
- Visual Acuity is impaired to moderate – severe
- Afferent Pupillary Defect is absent or mild

Fundus

- Tortuous and dilatation of all branches of Central Retinal Vein , Dot & Blot Hge, Flame shaped Hge throught all 4 quadrants
- Cotton wool spot, optic disc and macular ocdema

FA shows delayed A – V transit time, good retinal capillary perfusion and late leakage

Course

- Most acute signs resolve Over 6 – 12 months

PROGNOSIS

- In case do not subsequently become Ischaemic the prognosis is good
- The main causes for poor vision is chronic macular oedema

TREATMENT

Laser Photocoagulation for macular ocdena is not beneficial

Following Therapies

1. Cannulation (TPA)
2. Intravitreal Avastin for Cystoid Macular Oedema
3. Optic Nerve Sheathotomy

ISCHAEMIC Central Retinal Vein Occlussion

Venus Obstruction

↓

Retinal Perfusion + Capillary Closure + Retinal Hypoxia

↓

Retinal Ischaemic

Neo Vascular Glaucoma

DIAGNOSIS

Presentation → Sudden and severe Visual Impairment

Visual Acuity → Counting Fingers

Afferent pupillary defect → Marked

FUNDUS

- Tortuous and engorgement of all branches of Central Retinal Vein; Extensive Dot & Blot Hge Flame Shaped Hge, Severe optic disc oedema + hyperaemia
- Cotton wool spots

FLUOROESCEIN ANGIOGRAPHY → Delay in A - V Transit time, Central masking by retnal Hge, Extensive areas of capillary non perfusion

ERG → is decreased

COURSE → Most acute signs resolve in 9 – 12 months

Residual findings → disc collaterals + Macular epiretinal gliosis + Pigmentary changes

PROGNOSIS

- Prognosis is poor due to Macular Ischaemia
- ↓
- RUBEOSIS IRIDIS

(2 -4 months) 100 day glaucoma

- Unless Vigrous Pan Retinal Photocoagluation is performed there is high risk of Neo Vascular Glaucoma

TREATMENT

- Laser Pan Retinal Photocoagluation should be performed in Rubeosis Iridis
- Application of 1500 – 3000 burns
- 0.5 → 0.1 Sec

C. AGE RELATED MACULAR DEGENERATION

I. INTRODUCTION

1. Definition

   a. Age Related Maculopathy →Aging Process Characterised by DRUSEN + Hyperpigmentation or depigmentation of RPE

b. Age related Macular Degeneration → Geographical Atrophy + Pigment Epithelial Detachment + Choroidal New Vessels + Fibroglial Scar

2. Risk Factors

(a) Age (b) ARM (c)Race (d) Family H/o (e) Cataract

3. DRUSEN →Abnormal material in Bruch's membrane and basal lamina of RPE(Yellow excesences beneath the RPE)

Types

(Small Hard /Large Soft / Drusenoid RPE detachment/Calcified)

FA → Hyperfluorescence is due to atroppy of RPE (hydrophilic)

→ Hyperfluoscence – hydrophobic lowlipid content

DD - Familial Dominant Drusen

- Hard exudates
- Type 3 Membranoproliferative glomeuronephritis

II. Atrophic Age related Macular Degeneration

DRY Age Related Macular degeneration → Atrophy of photoreceptor + RPE + Choriocapillaries.

Signs Focal Atrophy of RPE

↓

Loss of choriocapillarics

↓

Enlargement of the Atrophic Areas

↓

With the larger choroidal vessels

FA → Hyperfluoroscence

Due to unmaking of background choridal Fluorescence

Treatment → LVA(Low vision Aids)

III. Retinal Pigment Epithelium Detachment

Pigment Epithelium Detachment

↓

Caused by reduction of Hydraulic conductivity of Bruch's Membrane

Signs →Dome shaped elevation

Sub RPE fluid is clear or Turbid

FA → Demarcated Oval area of Hyperfluroscence due to pooling of dye under the detachment

OCT → Separation of RPE from Bruch's membrane by fluid

COURSES

- Spontaneous Resolution
- Geographic Atrophy
- Detachment of the Sensory Retina
- RPE Tear formation

IV. RETINAL PIGMENT EPITHELIAL TEAR

A tear of RPE may occur at the junction of attached and detached RPE, Tears may occur Spontanously following laser Photocoagulation of CNV

Signs → Crescent Shaped RPE dehiscence

FLUOROSCEIN ANGIOGRAPHY →

I. CNV in the early phase

II. Late Phase → Hypoflouroscence (flap folded over & thickened RPE

III. Hyperfluoroscence → Exposed choriocapillares

OCT

- Loss of the normal dome shaped profile of the RPE in Pigment Epethelium Detachment

Prognosis

- Poor in subfoveal tears

V. NEOVASCULAR ARMD

Pathogenesis

- Neovascular ARMD caused by Choroidal New Vessels originated from the choriocapillaries through the defects in Bruch's membrane
- Intial visual loss associated CNV caused by blood under the Retina (SRF), into the retina (Macular odema) and under the RPE (PED)

Clinical Features

Presentation → Positive Scotomata & blurring of Vision due to fluid leakage from CNV

Signs

- Sub RPE (type1) CNV appears as grey – green
- subretinal (type2) CNV forms a subretinal Halo
- Serous Retinal elevation, Fovealthickening, CMO, Hard exudates

FA

I. Classic CNV → Lacy Pattern
   - Extra Foveal
   - Juxta Foveal
   - Sub Foveal

II. Occult CNV

III. Fibrovascular PED (CNV + PED) → Hot Spot

Course Prognosis is poor

Complications: Hge PED, VT Hge, SR Scarring, Massive exudation

TREATMENT

I. PhotoDynamic Threapy → VERTEPORFIN

   Defnitive Indications → SF Classic CNV

   Probable Indications → Small, Pure occult lesions

Possible Indications → Large occult lesions

Contra Indications → PED

Technique VPF 6mg/kg – 10 min

Laser is applied to CNV – 83 Sec

II. Anti – Arteriogenic Therapy

- Intravitreal steroids

- Anti – VEGF

a. Avastin

b. Lucentis

c. Macugen

III. Surgery - Submacular Surgery

- Macular Translocation

II. ANGIOGENESIS

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Further information: Fibroblast Growth Factor

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VEGF (Vascular Endothelial Growth Factor)

VEGF (Vascular Endothelial Growth Factor) has been demonstrated to be a major contributor to angiogenesis, increasing the number of capillaries in a given network. Initial in Vitro studies demonstrated that bovine capillary endothelial cells will proliferate and show signs of tube structures upon stimulation by VEGF and b FGF, although the result were more pronounced with VEGF. Upregulation of VEGF is a major component of the physiological response to exercise and its

role in angiogenesis is suspected to be a possible treatment in vascular injuries. In vitro studies clearly demonstrate that VEGF is a potent stimulator of angiogenesis because in the presence of this growth factor plated endothelial cells will proliferate and migrate, eventually forming tube structures resembling capillaries. VEGF causes a massive signaling cascade in endothelial cells. Binding to VEGF receptor -2 (VEGFR-2) starts a tyrosine kinase signaling cascade that stimulates the production of factors that variously stimulate vessel permeability (eNoS, producing NO), proliferation/survival (Bfgf), migration (ICAMSNCAMs/MMPs) and finally differentiation into mature blood vessels. Mechanically, VEGF is upregulated with muscle contractions as a result of increased blood flow to affected areas. The increased flow also causes a large increase in the m RNA production of VEGF receptors 1 and 2. The increase in receptor production means that muscle contractions could cause upregulation of the signaling cascade relating to angiogenesis. As part of the angiogenic signaling cascade, NO is widely considered to be a major contributor to the angiogenic response because inhibition of NO significantly reduces the effects of angiogenic growth factors. However, inhibition of NO during exercise does not inhibit angiogenesis indicating that there are other factors involved in the angiogenic response.

Angiopoietins

The angiopoietins, Angl and Ang2, are required for the formation of mature blood vessels, as demonstrated by mouse knock out studies. Ang 1 and Ang 2 are protein growth factors which act by binding their receptors. Tie-l and Tie-2, while this is somewhat controversial, it seems that cell signals are transmitted mostly by

Tie-2, though some papers show physiologic signaling via Tie-l as well. These receptors are tyrosine kinases. Thus, they can initiate cell signaling when ligand binding causes a dimerization that initiates phosphorlation on key tyrosines.

MATRIX METALLO PROTEINASE

Another major contributor to angiogenesis is matrix metallo proteinase (MMP). MMPs help degrade the proteins that keep the vessel walls solid. This proteolysis allows the endothelial cells to escape into the interstitial matrix as seen in sprouting angiogenesis. Inhibition of MMPs prevents the formation of new capillaries. These enzymes are highly regulated during the vessel formation process because destruction of the extracellular matrix would decrease the integrity of the microvasculature.

IV ANGIOGENESIS PATHWAY

Vascular endothelial growth factor (VEGF) plays a key role in physiological blood vessel formation. Hypoxia is a potent inducer of VEGF in vitro, The increase in secreted biologically active VEGF protein from cells exposed to hypoxia is partly because of an increased transcription rate, mediated by binding of hypoxia-inducible factor-l (HIFl) to a hypoxia responsive element in the 5'-flanking region of the VEGF gene, bHLH-PAS transcription factor that interacts with the Ah receptor nuclear translocator (Arnt), and its predicted amino acid sequence exhibits significant similarity to the hypoxia-inducible factor l alpha (HIFla) product, HLF mRNA expression is closely correlated with that of VEGF

mRNA.. The high expression level of HLF mRNA in the 02 delivery system of developing embryos and adult organs suggests that in a normoxic state, HLF regulates gene expression of VEGF, various glycolytic enzymes, and others driven by the HRE sequence, and may be involved in development of blood vessels and the tubular system of lung, VEGF expression is dramatically induced by hypoxia due in large part to an increase in the stability of its mRNA, HuR binds with high affinity and specificity to the VRS element that regulates VEGF mRNA stability by hypoxia. The secreted VEGF is a major angiogenic factor that regulates multiple endothelial cell functions, including mitogenesis. Cellular and circulating levels of VEGF are elevated in hematologic malignancies and are adversely associated with prognosis. Angiogenesis is a very complex, tightly regulated, multistep process, the targeting of which may well prove useful in the creation of novel therapeutic agents. Current approaches being investigated include the inhibition of angiogenesis stimulants (e.g., VEGF), or their receptors, blockade of endothelial cell activation, inhibition of matrix metallo proteinases.

V. AVASTIN IN DETAIL

Bevacizumab is an immunoglobulin G (IgG) composed of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N-linked oligosaccharide and has a molecular weight of approximately 149,000 daltons.

DESCRIPTION

AVASTIN is a clear to slightly opalescent, colourless to pale brown sterile solution for intravenous (IV) infusion. AVASTIN is available in 100 mg and 400 mg single dose vials containing 4 mL and 16 mL, respectively of bevacizumab (25 mg/mL). AVASTIN also contains a trehalose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

PHARMACOLOGY

Mechanism of Action

AVASTIN is an antineoplastic agent containing the active ingredient, bevacizumab. Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium

containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at <= 0.35 ppm.

AVASTIN inhibits the binding of VEGF to its receptors, Flt-l and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive antitumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

PHARMACOKINETICS

The pharmacokinetics of bevacizumab were characterised in patients with various types of solid tumours. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (V_C), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and subject age [the median age was 59 years with 5^{th} and 95^{th} percentiles of 37 and 76 years]).

Low albumin and high alkaline phosphatase levels are generally indicative of disease severity and tumour burden. Bevacizumab clearance was approximately 20% higher either in subjects with low levels of serum albumin or in subjects with elevated alkaline phosphatase levels when compared with the typical subject with median values of albumin and/or alkaline phosphatase.

Distribution

The typical value for Vc was 2.66 L and 3.25 L for female and male subjects, respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. After correcting for body weight, male subjects had a larger Vc (+22%) than females.

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of ^{125}1- bevacizumab suggested that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.

Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk.

The value for clearance is, on average, equal to 0.207 and 0.262 L/day for female and male subjects, respectively. After correcting for body weight, male subjects had a higher bevacizumab clearance (+26%) than females. According to the bi-compartmental model, the initial half-life (α) is 1.4 days for both sexes, and the terminal (β) half-life estimate is 20 days for a typical female subject and 19 days for a typical male.

Pharmacokinetics in Special Populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Children and Adolescents: No formal studies have been conducted to examine the pharmacokinetics of bevacizumab in children and adolescent patients.

Renal impairment: No formal studies have been conducted to examine the pharmacokinetics of bevacizumab in subjects with renal impairment.

Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of bevacizumab in subjects with hepatic impairment.

VI. AVASTIN IN VARIOUS DISEASES

PROLIFERATIVE DIABETIC RETINOPATHY

Haritoglou C and et al., 2006 evaluated the efficacy of bevacizumab for the treatment of diabetic macular edema in 51 consecutive patients (26 females and 25 males; mean age, 64 years) with diffuse diabetic macular edema. Inclusion criteria were determined independently of the size of edema, retinal thickness, visual acuity, age, metabolic control, type of diabetes, or previous treatments beyond a 6-month period. All patients had undergone previous treatments, such as focal laser therapy (35%), full-scatter panretinallaser therapy (37%), vitrectomy (12%), and intravitreal injection of triamcinolone (33%). Changes in ETDRS letters were not significant throughout follow-up. Mean retinal thickness +/- SD decreased to 425 +/- 180 micro m at 2 weeks (P = 0.002), 416 +/- 180 micro m at 6 weeks (P = 0.001), and 377 +/117 micro m at 12 weeks (P = 0.001). Changes of retinal thickness and visual acuity correlated weakly (r = -0.480 and P = 0.03 at 6 weeks; r = -0.462 and P = 0.07 at 12 weeks). The increase of visual acuity after 6 weeks as measured by ETDRS charts could be predicted best by baseline visual acuity. No other factors investigated, such as age, thickness by optical coherence tomography, or previous treatments, were predictive for the increase in visual acuity.

Hence diffuse diabetic macular edema not responding to previous treatments such as photocoagulation, intravitreal injection of triamcinolone, or vitrectomy, improvement of visual acuity and decrease of retinal thickness could be observed after intravitreal injection of bevacizumab. Although our follow-up period was

too short to provide specific treatment recommendations, the short-term results encourage further prospective studies with different treatment groups and longer follow-up.

CENTRAL RETINAL VEIN OCCLUSION

Costa RA and et al., 2007 evaluated the safety, visual acuity changes, and morphologic effects associated with intravitreal bevacizumab injections for the management of macular edema due to ischemic central retinal vein occlusion (CRVO). In this prospective, open-label study, 7 consecutive patients (7 eyes) with macular edema associated with ischemic central or hemicentral RVO were treated with intravitreal injections of 2.0 mg (0.08 mL) of bevacizumab at 12-week intervals.

The median age of the 7 patients was 65 years (range, 58-74 years), and the median duration of symptoms before injection was 7 months (range, 2.5-16 months). At baseline, mean BCVA was 1.21 (Snellen equivalent, approximately 20/320) in the affected eye. Mean baseline CMT and TMV were 730.1 microm and 17.1 mm (3), respectively. Fluorescein leakage was observed in the macula and affected retinal quadrants in all seven eyes. Six patients completed the 25-week follow-up examination with reinjections performed at weeks 12 and 24. The most common adverse events were conjunctival hyperemia and subconjunctival hemorrhage at the injection site. At the last follow-up, mean BCVA in the affected eye was 0.68 (Snellen equivalent, 20/100(+1). No patient had a decrease in BCVA. Mean CMT and TMV at the 25-week follow-up were 260.3 micron and

9.0 mm(3), respectively; fluorescein leakage within the macula and affected retinal quadrants as compared with baseline was markedly reduced in all patients. Coupled with fluorescein angiographic findings, OCT data suggest a trend of macular edema recurrence between 6 weeks and 12 weeks after injection.

Hence Intravitreal bevacizumab injections of 2.0 mg at 12-week intervals were well tolerated and were associated with short-term BCVA stabilization or improvement and favourable macular changes in all patients with ischemic RVO and associated macular edema.

AGE-RELATED MACULAR DEGENERATION

Goff MJ and et al., 2007 reported the optical coherence tomography (OCT) findings and visual results in a series of patients treated with intravitreal bevacizumab for choroidal neovascularization (CNV) associated with age-related macular degeneration (ARMD), and to determine if a difference in treatment effect exists between previously treated and treatment patients. A retrospective review of all patients treated with intravitreal bevacizumab for CNV from ARMD with visual acuity greater than or equal to 20/320 between September 2005 and February 2006 was performed. Fifty-four eyes of 51 patients treated with intravitreal bevacizumab for CNV from ARMD were identified. A total of 178 injections were performed. Mean number of days of follow-up was 138 with 91 % of patients having at least 90 days of follow-up. Seventy percent of patients had undergone previous treatment for CNV. The mean number of intravitreal bevacizumab injections per eye was 3.3. Combined treatment with photodynamic

therapy was provided in 20% of cases at the initial intravitreal injection. OCT data for all patients revealed an initial mean thickness of 362 mum, which was decreased at 1 week to 278 micron (P = 0.001), 235 micron at 1 month (P<0.0001), 238 micron at 3 months (P = 0.0004), and 244 micron for the end of follow up (P < 0.0001). Cystic retinal edema, subretinal fluid, and pigment epithelial detachment resolved in the majority of cases, but pigment epithelial detachment frequently took longer to resolve. Initial mean visual acuity was 20/125 (logMAR 0.8), and final mean visual acuity was 20/100 (logMAR 0.7) (P = 0.03). There was no difference in OCT or visual acuity outcomes (P = 0.62 and P = 0.28, respectively) between previously treated and treatment naIve patients. There was no difference in OCT or visual acuity outcomes (P = 0.67 and P = 0.21, respectively) between patients who received combination therapy and those who received monotherapy with intravitreal bevacizumab. No systemic or ocular adverse events were recorded. Hence Intravitreal bevacizumab for CNV from ARMD results in a rapid decrease in OCT-measured retinal thickness in a majority of cases. Visual acuity also improved in this series, suggesting a potential corresponding visual benefit. This series suggests that previously treated and treatment naive patients have similar outcomes.

VII. Complication of Intraviteral Injection of Avastin

Complication of Intraviteral Injection of Avastin
General Complications • Cataract • Glaucoma • Vitreous Heemorrhage • Retinal detachment • Endophthalmitis Specific Complications • Retinal pigment epithelial rip • Submacular haemorrhage • Progression of tractional retinal detachment • Visual hallucinations • Metrorrhagia

Patients and Methods

PATIENTS AND METHODS

This prospective, interventional study was done at Retina Clinic, Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli from June 2007 to July 2008.

Inclusion Criteria

1 Patients with Proliferative Diabetic Retinopathy

2 Patients with retinal vein occlusion and neovascularization

3 Patients with wet Age related Macular Degeneration

Exclusion Criteria

1. Presence of other retinal pathaology affecting Visual Acuity
2. Presence of Significant cataract

Complete medical and ocular history was taken in the baseline visit. All patients underwent a complete ophthalmic examinations which include:

1 Best corrected distant and near vision

2 Intraocular pressure

3 Slit lamp examination

4 Fundus examination

5 Fundus photography

6 Fundus Fluorescein Angiography

7 Macular thickness with OCT

Procedure

All patients were informed of the procedure, the possible complications and informed consent was obtained. The institute ethics committee approved the study.

Peribulbar anaethesia was given. 2 drops of 5% Povidone – Iodine were instilled in the eye followed by through cleaning of the eye lashes and application of lid speculum.

0.1 ml (4 mg) of Bevacizumab (Roche India Ltd, Mumbai, India) was drawn in a 2 cc syringe and fitted with 26 g (1/2 inch) needle. The injection site was usually the inferotemporal quadrant to avoid drug deposition in front of the visual axis. The site of injection was 3.5 mm and 4 mm from limbus in pseudophakic and phakic eyes respectively. The needle was introduced downwards and backwards with the bevel of the needle facing anteriorly. This was done to avoid contact of the drug with macula. After injection, the needle was removed simultaneously with the application of a cotton tipped applicator over its entry site to prevent regurgitation of the inject material. One drop of topical antibiotic solution was administered and the eye was patched.

The patient was made to sit up immediately after injection and continue maintaining erect posture for atleast 6 hours. All patients were started on capsule acetazolamide (sustained release) 500 mg two times a day for 3 days, 0.5%

timolol maleate eye drops twice daily for 1 month and antibiotic eye drops 6 times a day for 1 week.

Follow up examination was done at 3 days, 2 weeks, 1 month and then at monthly intervals for 6 months.

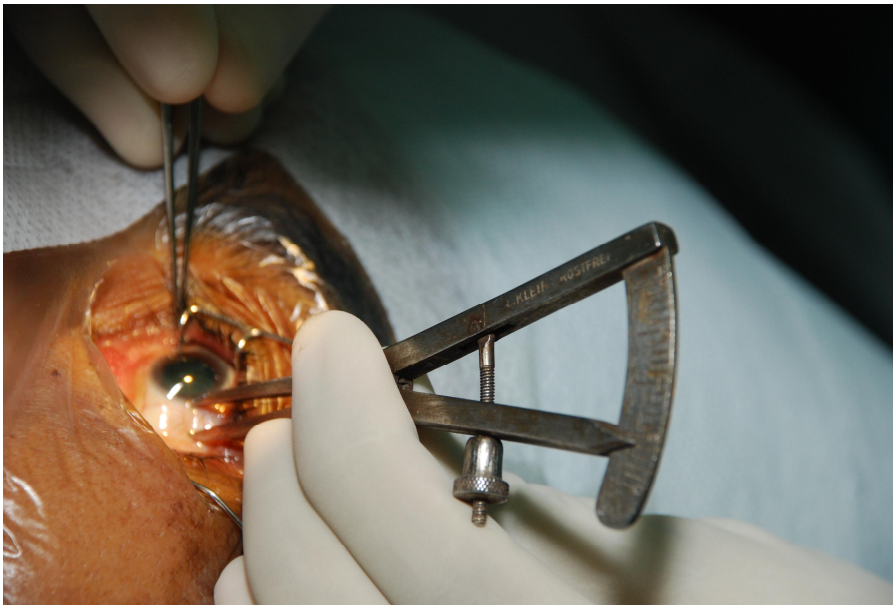
On follow up the examinations done were:

1. Best corrected distant and near vision
2. Intraocular pressure
3. Slit lamp examination
4. Fundus examination
5. Fundus photography
6. Macular thickness with OCT
7. Fundus Fluorescein Angiography

The Main outcome measures are:

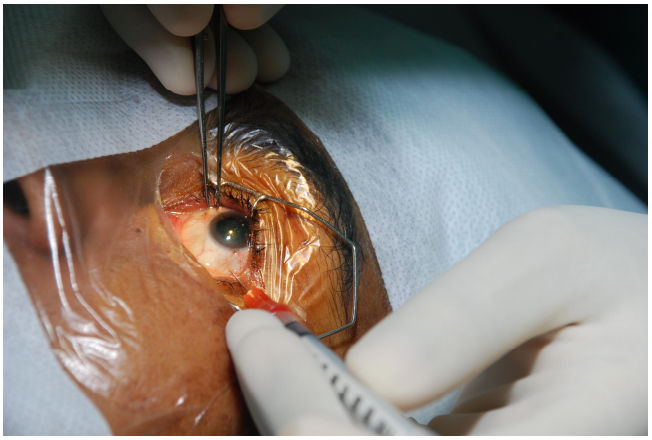
- Visual Acuity / regression of new vessels

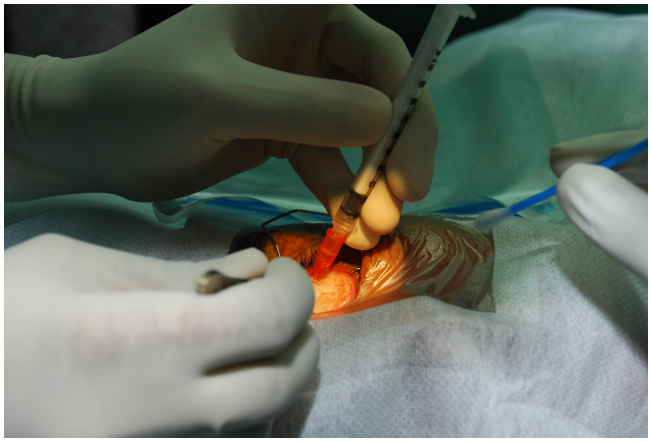
Bevacizumab preparation

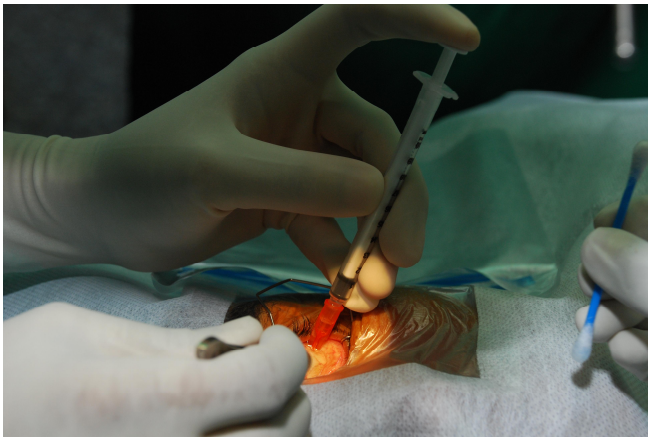


Caliper Showing 4 mm from the Limbus

BEVACIZUMAB INJECTED INTO THE EYE







Results

RESULTS

50 Eyes of 50 patients received an intravitreal injection of 4 mg (0.1 ml) of Bevacizumab (Avastin) during the study period (June 2007 to July 2008). Induded Diabetic Retinopathy, Branch Retinal Vein Occlusion, Central Retinal Vein Occlusion, Age related Macular Degeneration.

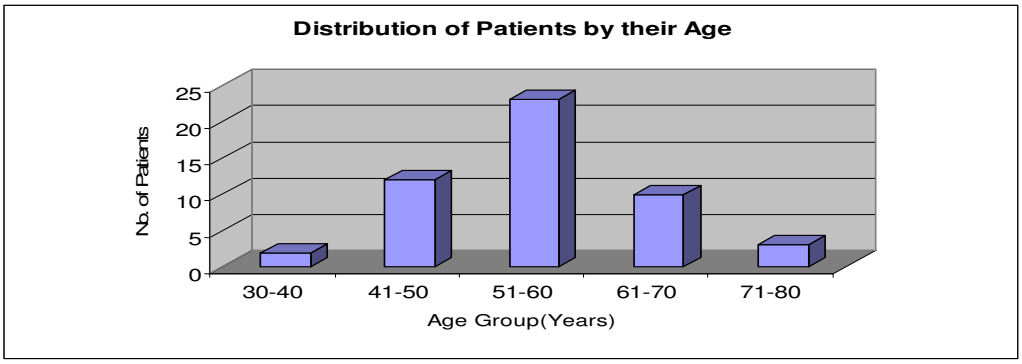
AGE DISTRIBUTION

Table – 1

Distribution of Patients by their Age

Age Group (Years)	No. of Patients	Percentage (%)
30-40	2	4
41-50	12	24
51-60	23	46
61-70	10	20
71-80	3	6
Total	50	100

Source: Master Chart



As seen in the age distribution 4% of patients were in the age group of 30-40 years, 24% patients were in the age group of 41-50 years, 46% of patients were in the age group of 51-60 years, 20% of patients were in the age group of 61-70 years and 6% of patients were in the age group of 71-80.

Majority of patients (46%) belonged to the Age group of 51 – 60. The youngest patient was 39 years of age and the eldest 75 years.

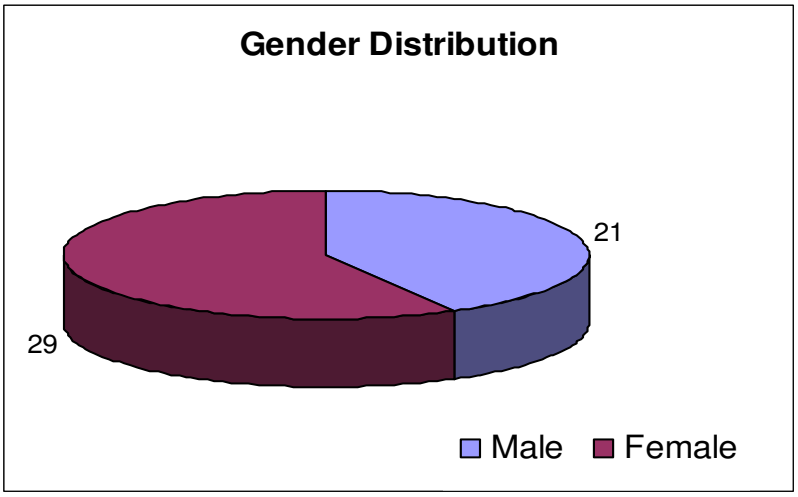
GENDER DISTRIBUTION

Table – 2

Distribution of Patients by their Gender

Gender	No. of Patients	Percentage (%)
Male	21	42
Female	29	58
Total	50	100

Source: Master Chart



As seen in the Gender distribution 42 %(21 out of 50) of patients are male and remaining 58% (29 out of 50) of patients are female.

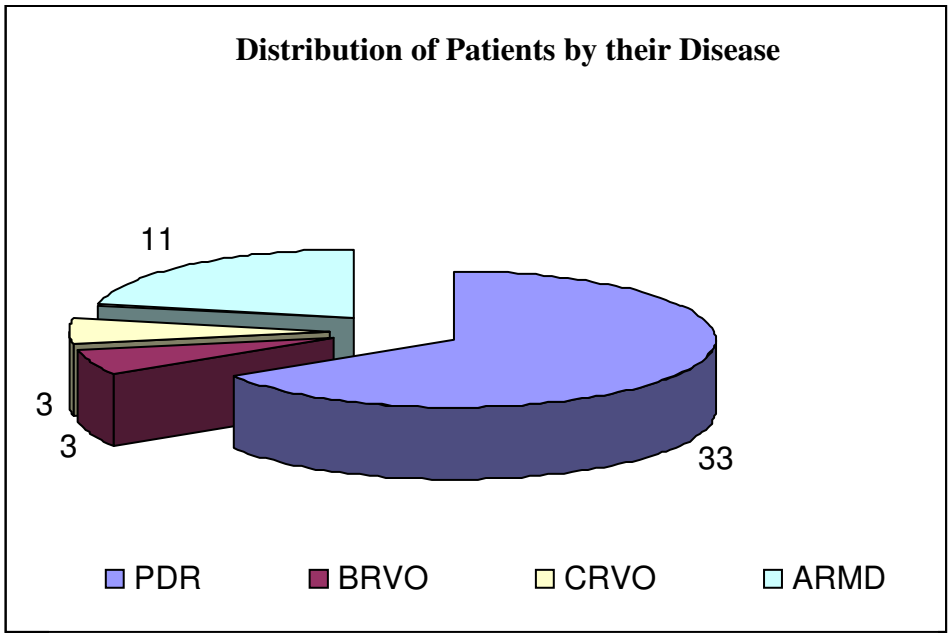
DISEASE DISTRIBUTION

Table – 3

Distribution of Patients by their Disease

Disease	No. of Patients	Percentage (%)
PDR	33	66
BRVO	3	6
CRVO	3	6
ARMD	11	22

Source: Master Chart



As seen in the Disease Distribution by patient wise was inferred that 66% of patients were suffered from PDR (Diabetic Retinopathy), 6% of patients were suffered from BRVO (Retinal Vein Occlusions), 6% of patients were suffered from CRVO (Central Retinal Vein Occlusions) and 22% of patients were suffered from ARMD (Age related Macular Degeneration).

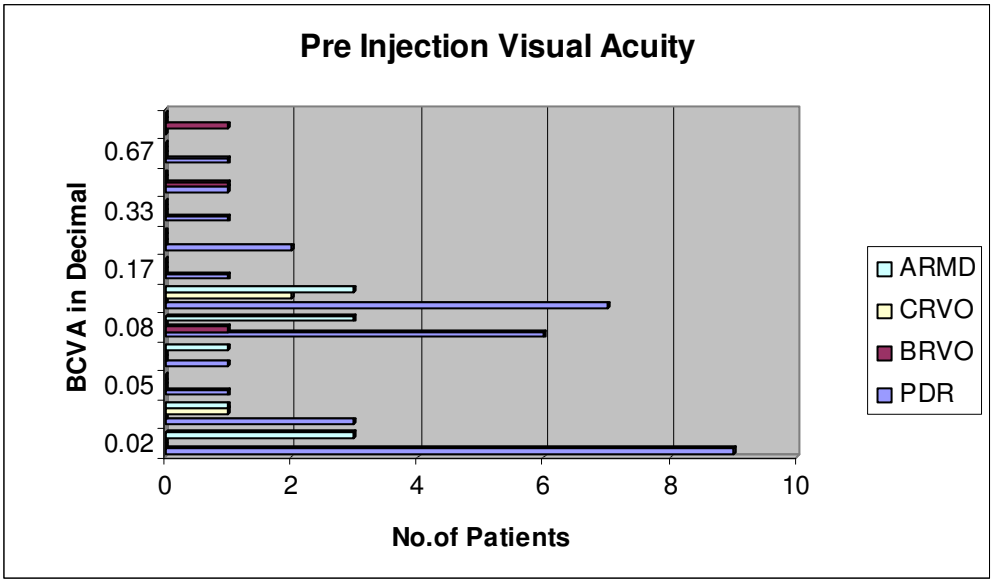
Pre Injection Best Visual Acuity

Table – 4

Distribution of Patients by Pre Injection Best Visual Acuity (BCVA)

Visual Acuity (in Decimal)	No. of Patients			
	PDR	BRVO	CRVO	ARMD
0.02	9	0	0	3
0.03	3	0	1	1
0.05	1	0	0	0
0.07	1	0	0	1
0.08	6	1	0	3
0.10	7	0	2	3
0.17	1	0	0	0
0.25	2	0	0	0
0.33	1	0	0	0
0.50	1	1	0	0
0.67	1	0	0	0
1.00	0	1	0	0

Source: Master Chart



As seen in the Pre injection Best visual Acuity distribution by patient wise was inferred that 12 No. of patients (PDR-9, BRVO -0, CRVO – 0, ARMD – 3) were affected by visual acuity at the level of 1/60(0.02 in decimal), 5 No. of patients (PDR-3, BRVO -0, CRVO – 1, ARMD – 1) were affected by visual acuity at the level of 2/60(0.03 in decimal), 1 No. of patient (PDR-1, BRVO -0, CRVO – 0, ARMD – 0) were affected by visual acuity at the level of 3/60(0.05 in decimal), 2 No. of patients(PDR-1, BRVO -0, CRVO – 0, ARMD – 1) were affected by visual acuity at the level of 4/60(0.07 in decimal).

10 No. of patients (PDR-6, BRVO -1, CRVO – 0, ARMD -3) were affected by visual acuity at the level of 5/60(0.08 in decimal), 12 No. of patients (PDR-7, BRVO -0,CRVO – 2, ARMD - 3) were affected by visual acuity at the level of 6/60(0.10 in decimal), 1 No. of patient (PDR-1, BRVO -0, CRVO – 0, ARMD – 0) were affected by visual acuity at the level of 6/36(0.17 in decimal).

2 No. of patients (PDR-2, BRVO -0, CRVO – 0, ARMD - 0) were affected by visual acuity at the level of 6/24(0.25 in decimal), 1 No. of patient (PDR-1, BRVO -0, CRVO – 0, ARMD – 1) were affected by visual acuity at the level of 6/18(0.33 in decimal) 2 No. of patients (PDR-1, BRVO -1, CRVO – 0, ARMD – 0) were affected by visual acuity at the level of 6/12(0.50 in decimal), 1 No. of patient (PDR-0, BRVO -1, CRVO – 0, ARMD – 0) were affected by visual acuity at the level of 6/9(0.67 in decimal) and 1 No. of patients (PDR-1, BRVO -0,CRVO – 0, ARMD – 0) were affected by visual acuity at the level of 6/6(1.00 in decimal).

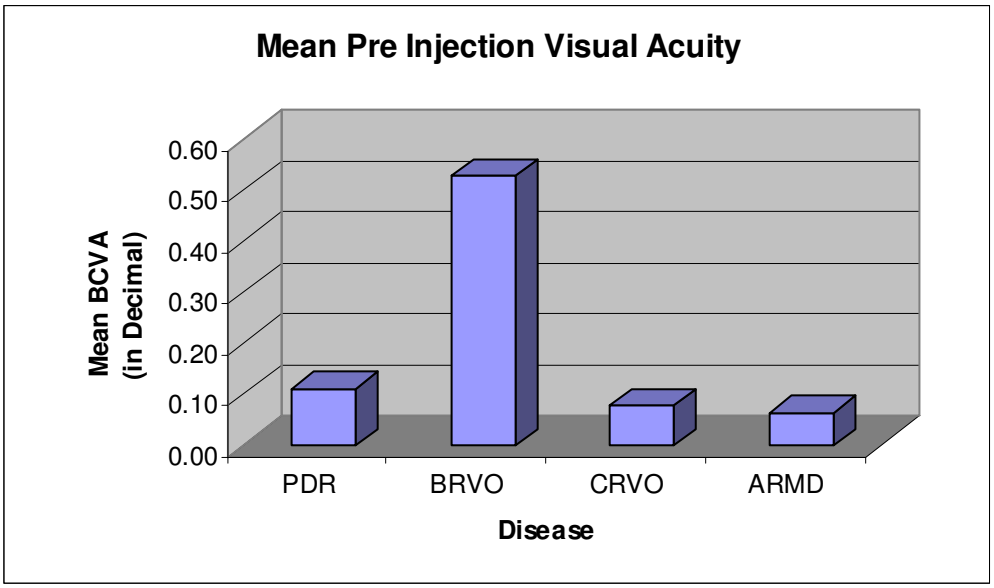
Pre Injection Visual Acuity Mean Value

Table -5

Mean Pre Injection Visual Acuity (BCVA)

Disease	Visual Acuity Mean Value (in Decimal)
PDR	0.11
BRVO	0.53
CRVO	0.08
ARMD	0.06

Source: Master Chart



As seen in the Pre injection Best visual Acuity distribution by disease wise was inferred that mean value for Pre injection Visual Acuity was 0.11 (in decimal) for PDR, that mean value for Pre injection Visual Acuity was 0.53 (in decimal) for BRVO, that mean value for Pre injection Visual Acuity was 0.08 (in decimal) for CRVO and that mean value for Pre injection Visual Acuity was 0.06 (in decimal) for ARMD.

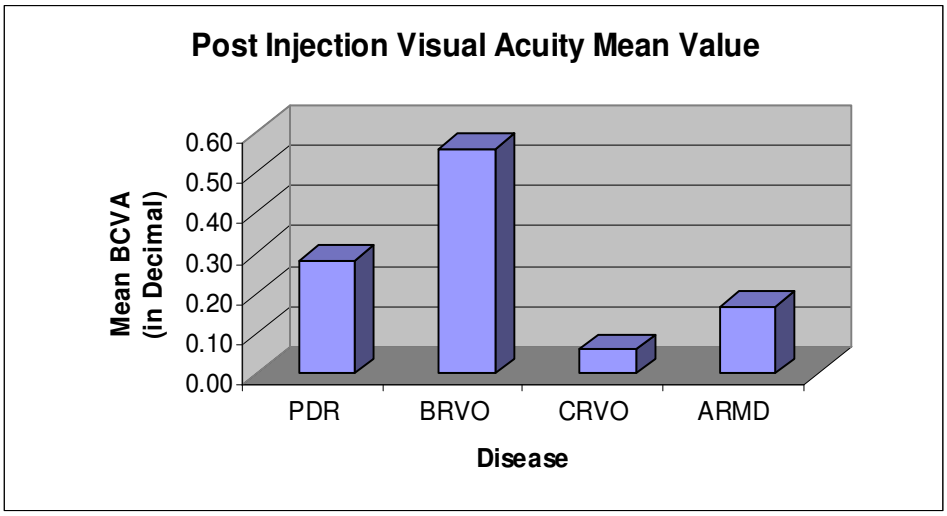
Post Injection Visual Acuity Mean Value

Table – 6

Mean Post Injection Visual Acuity

Disease	Visual Acuity Mean Value (in Decimal)
PDR	0.28
BRVO	0.56
CRVO	0.06
ARMD	0.17

Source: Master Chart



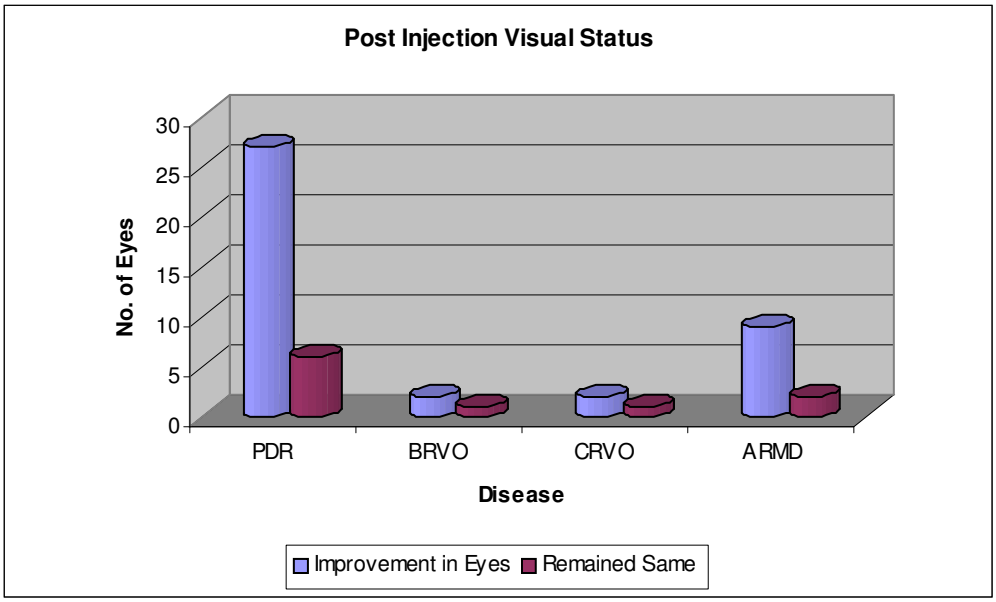
As seen in the Post injection Best visual Acuity distribution by patient wise was inferred that the mean value of post injection of Best Visual Acuity was 0.28 (PDR), 0.56(BRVO), 0.06 (CRVO) and 0.17 (ARMD). After the 2 weeks interval period all the mean value indicated that the vision was improved. The highest mean value of Best Visual Acuity Right eye was 0.56 decimal (CRVO decimal).

Post Injection improvement Visual Status

Table – 7

Post injection Visual Status, Disease Wise

Disease	Improvement in Eyes	Remained Same
PDR	27	6
BRVO	2	1
CRVO	2	1
ARMD	9	2



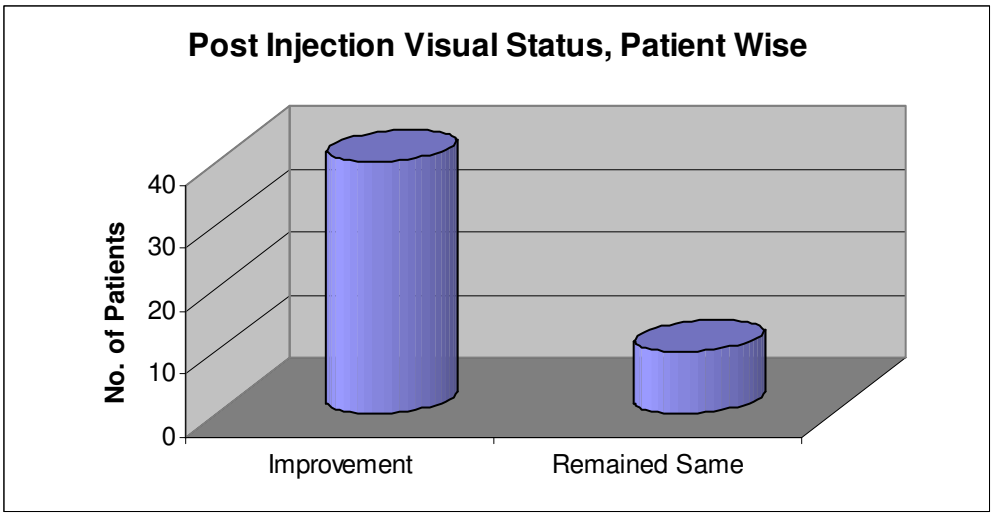
As seen in the Post injection Best visual Acuity improvement distribution by disease wise was inferred that 27 No. of eyes in PDR, 2 No. of eyes in BRVO, 2 No. of eyes in CRVO and 9 No. of eyes in ARMD had improved by post injection against visual status, Disease. 6 No. of eyes in PDR, 1 No. of eye in BRVO, 1 No. of eye in CRVO and 2 No. of patients were in same condition.

Distribution of Post Injection improvement Visual Status

Table – 8

Post Injection Visual Status, Patient Wise

Visual Status	Improvement (No. of Patients)	Percentage (%)
Improvement	40	80
Remained Same	10	20



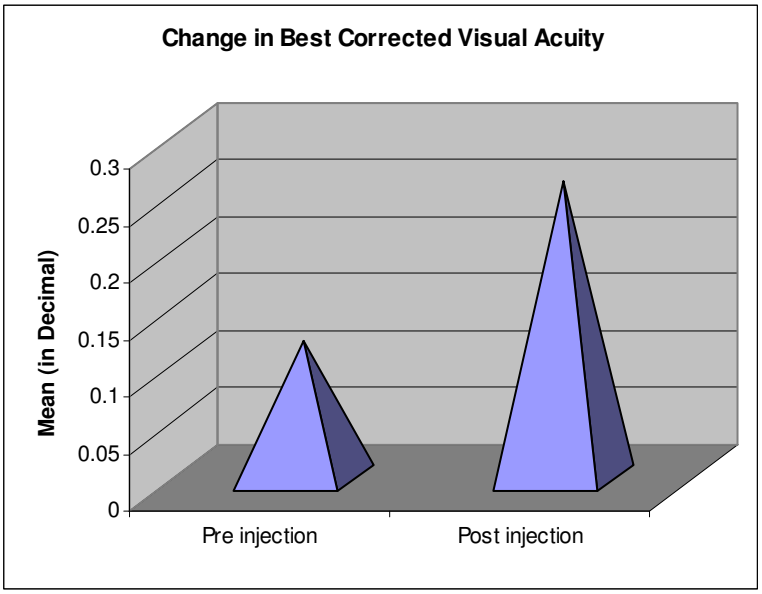
As seen in the Post injection Best visual Acuity improvement distribution by patient wise was inferred that 80% of Patients Visual Acuity status was improved after the post injection period and 20% of patients were remained in same position.

Pre and Post Injection Periodical BCVA

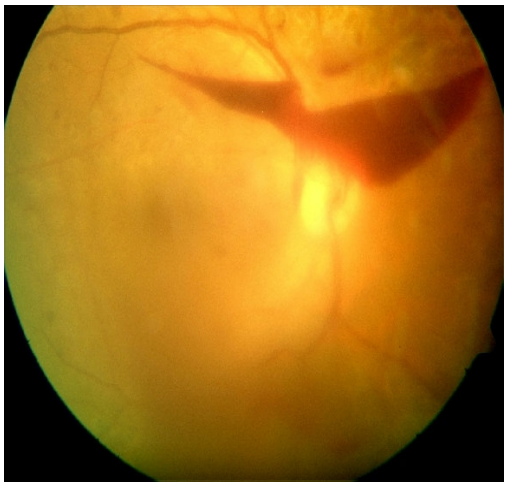
Table - 9

Change in Best Corrected Visual Acuity (BCVA)

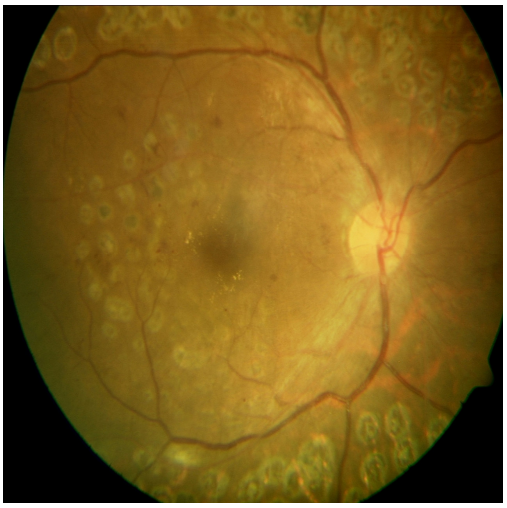
Period	Mean BCVA (in Decimal)	P value (T Test)
Pre injection	0.12	
Post injection	0.26	0.001



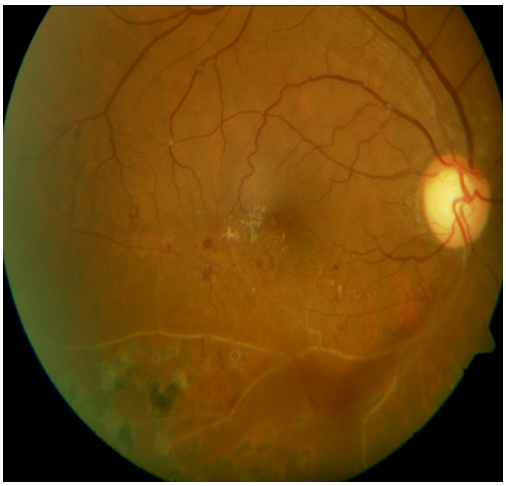
As seen in the Post injection Change Best visual Acuity was inferred that there is statistically significant relationship between periodical injection and improvement. In the subsequent visits, the improved vision was statically significant (p=0.001).



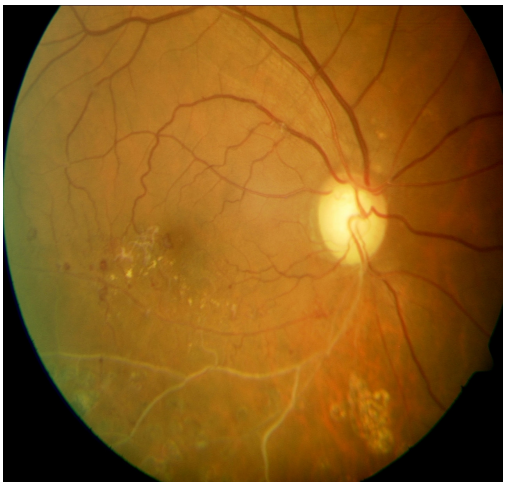
Pre Injection (PDR) Diabetic Retinopathy



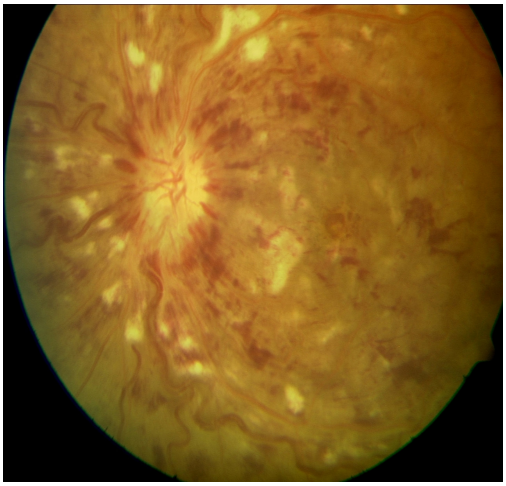
Post Injection (PDR) Diabetic Retinopathy



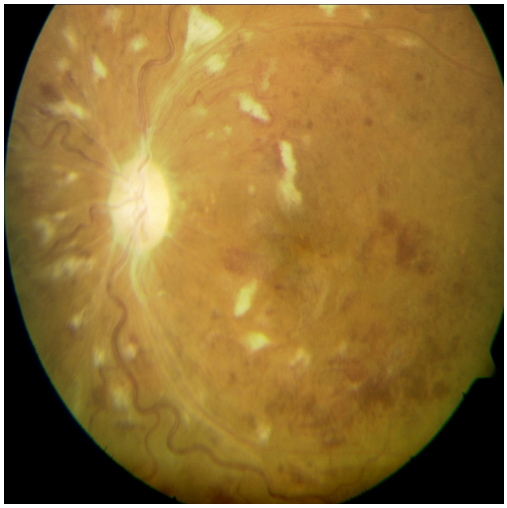
Pre Injection (BRVO) Retinal Vein Occlusion



Post Injection (BRVO) Retinal Vein Occlusion



Pre Injection (CRVO) Central Retinal Vein Occlusion



Post Injection (CRVO) Central Retinal Vein Occlusion

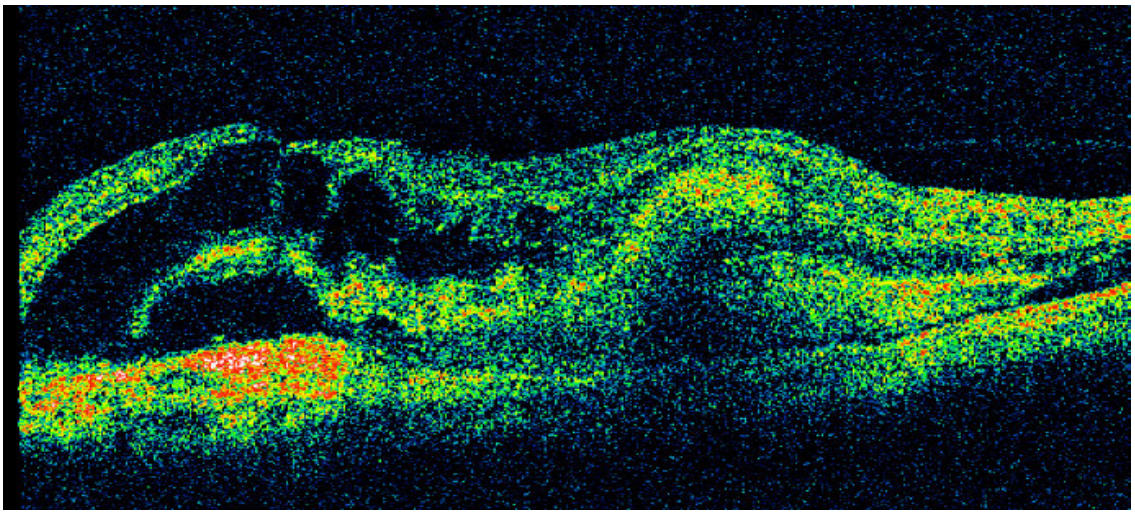
Pre Injection (ARMD) Age related Macular Degeneration

Post Injection (ARMD) Age related Macular Degeneration

Age related Macular Degeneration (ARMD)

Fundus Photography

FFA

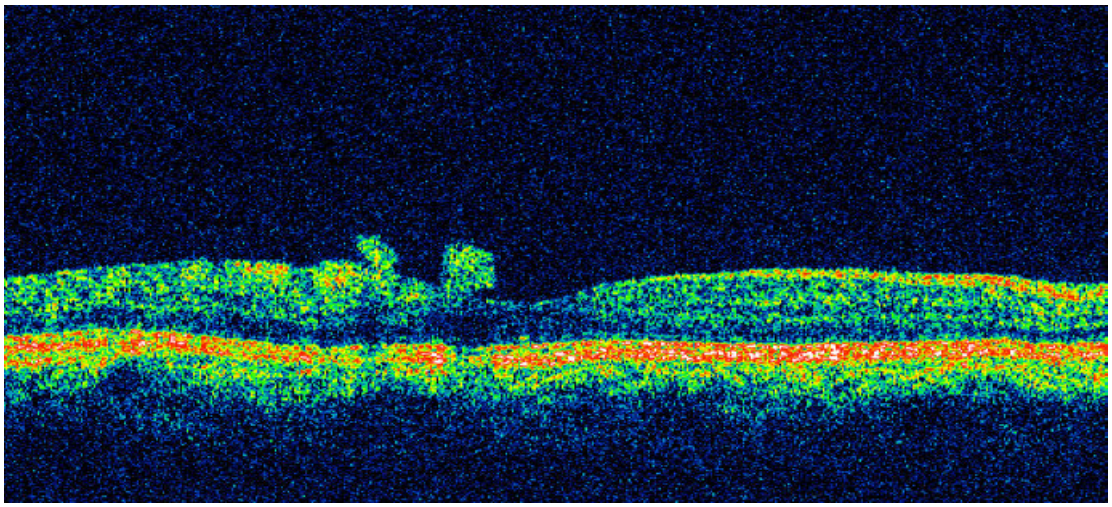


OCT

Retinal Vein Occlusions (BRVO)

Fundus Photography

FFA



OCT

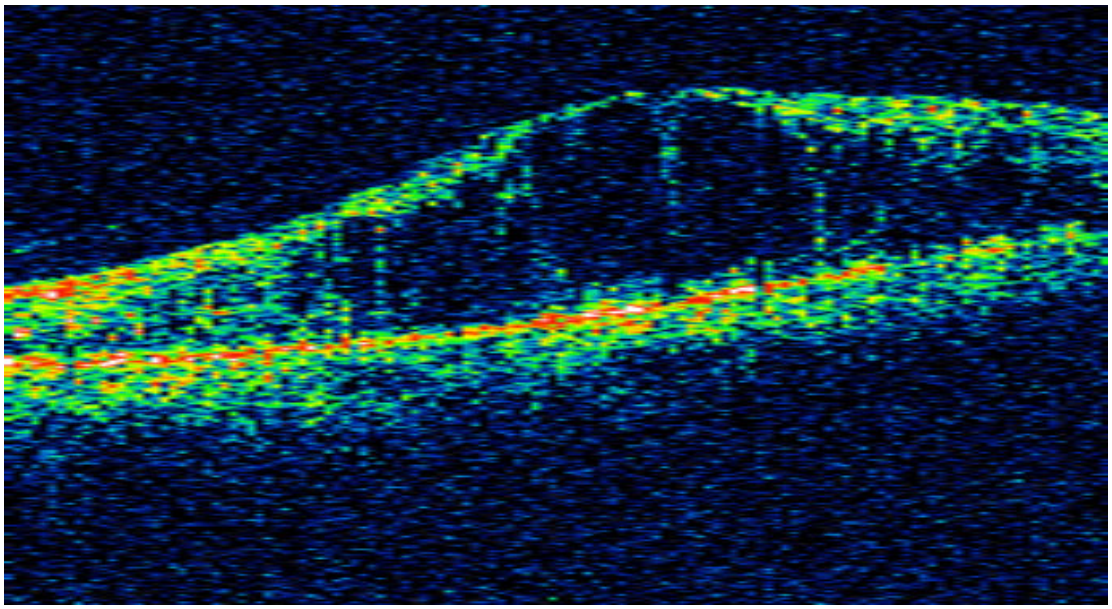
Diabetic Retinopathy (PDR)

Fundus Photography **FFA**

Central Retinal Vein Occlusions (CRVO)

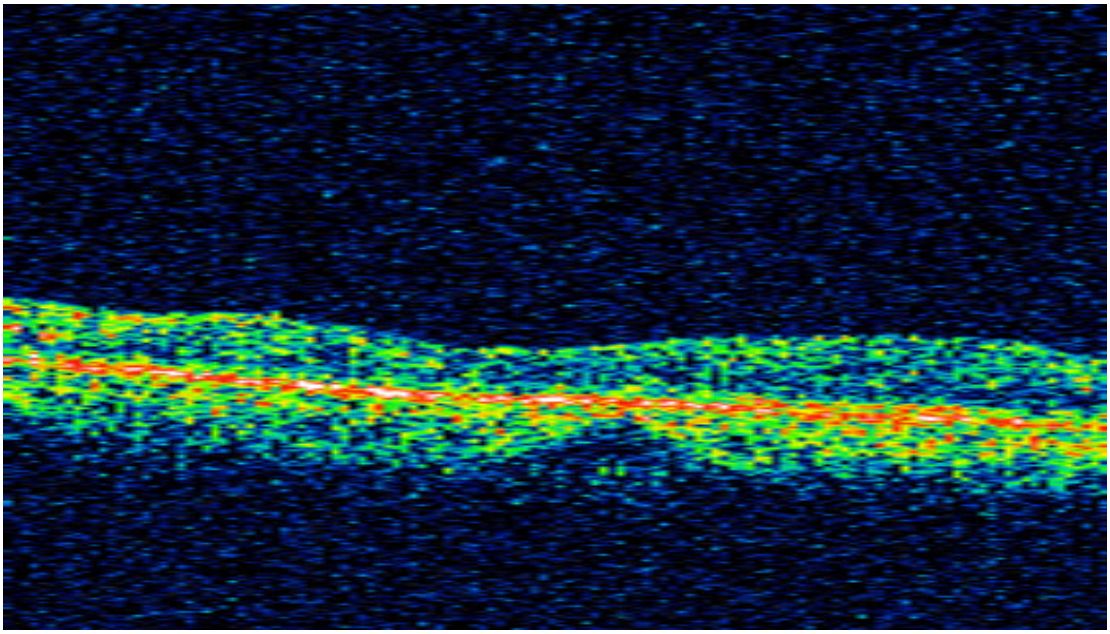
Fundus Photography **FFA**

Pre Injection Central Retinal Vein Occlusions (CRVO)



OCT

Post Injection Central Retinal Vein Occlusions (CRVO)



OCT

Discussion

DISCUSSION

PROLIFERATIVE DIABETIC RETINOPATHY

Haritoglou C and et al., 2006 evaluated the efficacy of bevacizumab for the treatment of diabetic macular edema in 51 consecutive patients (26 females and 25 males; mean age, 64 years) with diffuse diabetic macular edema. Inclusion criteria were determined independently of the size of edema, retinal thickness, visual acuity, age, metabolic control, type of diabetes, or previous treatments beyond a 6-month period. All patients had undergone previous treatments, such as focal laser therapy (35%), full-scatter panretinallaser therapy (37%), vitrectomy (12%), and intravitreal injection of triamcinolone (33%). . Changes in ETDRS letters were not significant throughout follow-up. Mean retinal thickness +/- SD decreased to 425 +/- 180 micro m at 2 weeks (P = 0.002), 416 +/- 180 micro m at 6 weeks (P = 0.001), and 377 +/117 micro m at 12 weeks (P = 0.001). Changes of retinal thickness and visual acuity correlated weakly (r = -0.480 and P = 0.03 at 6 weeks; r = -0.462 and P = 0.07 at 12 weeks). The increase of visual acuity after 6 weeks as measured by ETDRS charts could be predicted best by baseline visual acuity. No other factors investigated, such as age, thickness by optical coherence tomography, or previous treatments, were predictive for the increase in visual acuity.

Hence diffuse diabetic macular edema not responding to previous treatments such as photocoagulation, intravitreal injection of triamcinolone, or vitrectomy, improvement of visual acuity and decrease of retinal thickness could be observed after intravitreal injection of bevacizumab. Although our follow-up period was

too short to provide specific treatment recommendations, the short-term results encourage further prospective studies with different treatment groups and longer follow-up.

In Present study showed, Diabetic Retinopathy in 50 eyes Pre injection Visual Acuity mean value was 0.11 (in decimal). The follow up in this study was at 3 days, 2 weeks, and 1 month at monthly interval for 6 months. The mean value in PDR is statically significant in almost all visits and post injection visual acuity mean value was 0.27 (in decimal). The present study showed an improvement in visual acuity in 27 eyes. In 6 eyes visual acuity remained the same position after the post injection.

CENTRAL RETINAL VEIN OCCLUSION

Costa RA and et al., 2007 evaluated the safety, visual acuity changes, and morphologic effects associated with intravitreal bevacizumab injections for the management of macular edema due to ischemic central retinal vein occlusion (CRVO). In this prospective, open-label study, 7 consecutive patients (7 eyes) with macular edema associated with ischemic central or hemicentral RVO were treated with intravitreal injections of 2.0 mg (0.08 mL) of bevacizumab at 12-week intervals.

The median age of the 7 patients was 65 years (range, 58-74 years), and the median duration of symptoms before injection was 7 months (range, 2.5-16 months). At baseline, mean BCVA was 1.21 (Snellen equivalent, approximately 20/320) in the affected eye. Mean baseline CMT and TMV were 730.1 microm

and 17.1 mm(3), respectively. Fluorescein leakage was observed in the macula and affected retinal quadrants in all seven eyes. Six patients completed the 25-week follow-up examination with reinjections performed at weeks 12 and 24. The most common adverse events were conjunctival hyperemia and subconjunctival hemorrhage at the injection site. At the last follow-up, mean BCVA in the affected eye was 0.68 (Snellen equivalent, 20/100(+1). No patient had a decrease in BCVA. Mean CMT and TMV at the 25-week follow-up were 260.3 micron and 9.0 mm(3), respectively; fluorescein leakage within the macula and affected retinal quadrants as compared with baseline was markedly reduced in all patients. Coupled with fluorescein angiographic findings, OCT data suggest a trend of macular edema recurrence between 6 weeks and 12 weeks after injection.

Hence Intravitreal bevacizumab injections of 2.0 mg at 12-week intervals were well tolerated and were associated with short-term BCVA stabilization or improvement and favourable macular changes in all patients with ischemic RVO and associated macular edema.

In Present study showed Central Retinal vein occlusions in 50 eyes Pre injection Visual Acuity in was 0.08 (in decimal). The follow up in this study was at 3 days, 2 weeks, and 1 month at monthly interval for 6 months. The mean value in CRVO is statically significant in almost visits and post injection visual acuity mean value was 0.06 (in decimal). The present study showed an improvement in visual acuity in 2 eyes. In 1 Eye visual acuity remained the same position after the post injection.

AGE-RELATED MACULAR DEGENERATION

Goff MJ and et al., 2007 reported the optical coherence tomography (OCT) findings and visual results in a series of patients treated with intravitreal bevacizumab for choroidal neovascularization (CNV) associated with age-related macular degeneration (ARMD), and to determine if a difference in treatment effect exists between previously treated and treatment patients. A retrospective review of all patients treated with intravitreal bevacizumab for CNV from ARMD with visual acuity greater than or equal to 20/320 between September 2005 and February 2006 was performed. Fifty-four eyes of 51 patients treated with intravitreal bevacizumab for CNV from ARMD were identified. A total of 178 injections were performed. Mean number of days of follow-up was 138 with 91 % of patients having at least 90 days of follow-up. Seventy percent of patients had undergone previous treatment for CNV. The mean number of intravitreal bevacizumab injections per eye was 3.3. Combined treatment with photodynamic therapy was provided in 20% of cases at the initial intravitreal injection. OCT data for all patients revealed an initial mean thickness of 362 mum, which was decreased at 1 week to 278 micron ($P = 0.001$), 235 micron at 1 month ($P<0.0001$), 238 micron at 3 months ($P = 0.0004$), and 244 micron for the end of follow up ($P < 0.0001$). Cystic retinal edema, subretinal fluid, and pigment epithelial detachment resolved in the majority of cases, but pigment epithelial detachment frequently took longer to resolve. Initial mean visual acuity was 20/125 (logMAR 0.8), and final mean visual acuity was 20/100 (logMAR 0.7) ($P = 0.03$). There was no difference in OCT or visual acuity outcomes ($P = 0.62$ and

P = 0.28, respectively) between previously treated and treatment naIve patients. There was no difference in OCT or visual acuity outcomes (P = 0.67 and P = 0.21, respectively) between patients who received combination therapy and those who received monotherapy with intravitreal bevacizumab. No systemic or ocular adverse events were recorded. Hence Intravitreal bevacizumab for CNV from ARMD results in a rapid decrease in OCT-measured retinal thickness in a majority of cases. Visual acuity also improved in this series, suggesting a potential corresponding visual benefit. This series suggests that previously treated and treatment naive patients have similar outcomes.

In Present study showed Age Related macular degeneration in 50 eyes Pre injection Visual Acuity in was 0.06 (in decimal). The follow up in this study was at 3 days, 2 weeks, and 1 month at monthly interval for 6 months. The mean value in ARMD is statically significant in almost visits and post injection visual acuity mean value was 0.25 (in decimal). The present study showed an improvement in visual acuity in 9 eyes. In 2 eyes visual acuity remained the same position after the post injection.

Summary

SUMMARY

The Study entitled "The role of Intravitreal Bevacizumab in the Management of Various Retinal Vascular Diseases" was conducted at Retina Clinic, Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli. A total of 50 eyes of 50 patients were studied.

Baseline ophthalmic examination included:

- Best corrected visual acuity
- IOP measurement
- Slit lamp examination
- Fundus examination (+90 D lens & Indirect Ophthalmoscopy)
- Fundus photography
- Macular thickness with OCT
- Fundus Fluorescein Angiography

Follow up was done at 3 days, 2 weeks, 1 month and then at monthly interval for six months.

Observations

- Maximum number of patients belongs to the age group of 51 – 60 years.
- Out of 50 respondents 29 were female and 21were male.
- 50 patients have received injection in one of the eyes.
- 33 cases had diabetic retinopathy, 3 cases were branch retinal vein occlusion and 3 cases also central retinal vein occlusion. 11 cases were Age related Macular Degeneration

- 50 eyes received 4 mg (0.1 ml) of Bevacizumab (Avastin)
- Vision improved in 40 eyes (80%) and 10 eyes (20%) were remained same
- Post injection visual acuity improvement was statistically significant after 1 month and in all the follow up visits thereafter.
- There was statistically significant relationship between periodical injection and improvement in visual acuity.
- PDR was seen in 33 patients. In 27 eyes were improved and 6 eyes were remained same.
- BRVO was seen in 3 patients. In 2 eyes were improved and 1 eye was remained same.
- CRVO was seen in 3 patients. In 2 eyes were improved and 1 eye was remained same.
- ARMD was seen in 11 patients. In 9 eyes were improved and 2 eyes were remained same.

Conclusion

CONCLUSION

- Bevacizumab appears to be effective in the management of various retinal vascular diseases.
- Improvement in best corrected visual acuity was statistically significant
- The effect of Bevacizumab appears to be transient, necessitating repeat injections in case of recurrences.
- Complication due to the procedure, such as vitreous hemorrhage and endophthalmitis are very rare.
- Bevacizumab seems to be safe therapeutic option in patients who are resistant to conventional laser photocoagulation.

Bibliography

BIBLIOGRAPHY

1. Burri, PH(2004). "Intussusceptive angiogenesis: its emergence, its characteristics, and its Significance". Dev Dyn. 231 (3). 474-88. doi: 10. 1002/dvdy. 20184.
2. Blaber, M., DiSalvo, J.Thomas K.A., X-ray crystal structure of human acidic fibroblast growth factor. Biochemistry 35. 2086 - 2094, 1996.
3. Bcde Prior, B.M., Yang, HoT., & Terjung. R.L What makes vessels grow with exercise training? J App Physiol 97. 1119-28, 2004.
4. Ding. Y.H., Luan, X.D., Li, J. Rafo1s, J.A., Guthinkonda, M. & Diaz, F.G. et al. Exerciseinduced overexpression of angiogenic factors and reduction of ischemialreperfusion injury in stroke. Curr Neurovasc Res. 1 : 411 - 20,2004.
5. Ema M et aI., A novel bHLH-PAS factor with close sequence similarity to hypoxia-inducible factor 1alpha regulates the VEGF expression and is potentially involved in lung and vascular development. Proc Natl Acad Sci USA. (1997) Apr 29;94(9):4273-8.
6. Folkman, J. Klagsbrun, M.Angiogenetic factors, Science 235 : 442-447, 1987
7. Folkman J. Fighting cancer by attacking its blood supply. Sci am. 275:150-154,1996
8. Folkman, J. angiogenic therapy of the heart. Circulation 97: 629, 1998
9. Fogarty M. finding ways to starve the canser seed: angiogenesis, Iymphangiogenesis, bone metastases are focuses of intense research. The scientist, may 27, 2002

10. Gnarra JR et aI., Post-transcriptional regulation of vascular endothelial growth factor mRNA by the product of the VHL tumor suppressor gene. Proc Natl Acad Sci USA. (1996) Oct 1;93(20): 10589-94.

11. Goto, f., Goto, K.., Weindel, K., & Folkman, J.Synergistic effects of vascular endothelial growth- factor and basic fibroblast growth factor on the proliferation and cord formation of bovine capillary endothelial cells within collagen gels. Lab Inves 69,508-17, 1993.

12. Giles FJ. The vascular endothelial growth factor (VEGF) signaling pathway: a therapeutic target in patients with hematologic malignancies. Oncologist. (2001);6 Suppl 5:32-9. Review.

13. Gavin, T.P. Robinson, C.B., Yeager, R.C., England, J.a., Nifong. LW., & Hickner, RC. Angiogenic growth factor response to acute systemic exercise in human skeletal muscle. J app. Physiol 961 19-24, 2004.

14. Humana Press, Totowa, NJ 2005. Disease, such as age-related macular degeneration, may be created by a local expansion of blood vessels, interfering with normal physiological processes.

15. Jack J. Kansci, 5th Edition.

16. Kornowaski R. Eptsstein. S.E., Leon, M.b.(Eds). Handbook of myocardial revascularization and angiogenesis. Martin Dunitz Ltd., London, 2000.

17. Khurana, R. simons, M. Insights ttom angiogenesis trials using fibroblast growth factor for advanced arteriosclerotic disease. Trends Cardiovasc. Med. 13: 116 - 122, 2003.

18. Kraus, R.M., Stallings, H.W., Yeager, R.C., & Gavin, T.P. Circulating plasma VEGF response to exercise in sedentary and endurance-trained men. lApp Physiol 96 : 19-24 2004.

19. Lloyd, P.G., Prior, B.M., Yang, H.T.!, & TeIjung, R.LAngiogenic growth factor expression in rat skeletal muscle in response to exercise training. Am J. Physiol Heart Circ Physiol 284 : 1668 -78 2003.

20. Levy NS, et aI., Hypoxic stabilization of vascular endothelial growth factor mRNA by the RNA-binding protein HuR. J Bioi Chem. (1998) Mar 13;273(11):6417-23.

21. Laham, R.J. Bairn, D. S., Angiogenesis and direct myocardial revascularization.

22. McMahon G. VEGF receptor signaling in tumor angiogenesis. Oncologist. 2000;5 SuppI1:3-1O. Review.

23. Omitz, D.M., Hoh, N. Fibroblast growth factors. Genome Bioi 2 : 1-12,2001.

24. Perhaps an inhibitor of angiogenesis: Endothelial integrins and angiogenesis, not so simple anymore

25. Rubanyi, G.M. (Ed.), angiogenesis in health and disease, M.Dekker, Inc., New York - basel, 2000

26. Raizada, M.k., Paton, J.F.R., Kasparov, S., Katovich, M.J. (Eds), Cardiovascular genomics. Humana Press. Totowa, N.J. 2005.

27. Stegmann, U. New Vessels for the Heart, Angiogenesis as New Treatment for Coronary Heart Disease. The story of its Discovery and Development. Henderson, Nevada, Carido Vasculr Bio Therapeutics Inc., 2004.

28. Schumacher, B., Pecher, P., Von Specht, B.U., Stegmann, t.J. Induction of neoangiogenesis in ischemic myocardium by human growth factors. Circulation 97: 645-650, 1998.

29. Stegmann, T.J. A human growth factor in the induction ofneoangiogenesis. Exp. Opin. Invest. Drugs 7: 2011-2015, 1998.

30. Stegmann, t.J., Hoppert, T., Schneider, A. Popp, M., Strupp, G., Thing, R.O., Hertel, A : Therapeutic angiogenesis intramyocardial growth factor delivery of FGF-1 as sole therapy in patients with chronic coronary artery disease. CVR 2000, 1 259-267

31. Stein I, et aI., Translation of vascular endothelial growth factor mRNA by internal ribosome entry: implications for translation under hypoxia. Mol Cell BioI. (1998) Jun;18(6):3112-9.

32. Thurston G. Role of Angiopoietins and Tie receptor tyrosine kinases in angiogenesis and lymphangiogenesis. Cell Tissue Res. 2003 Oct. 314 (1) 61-8 Epub 2003 Aug 12.

33. Vascular endothelial growth factor. Mini-reviews & technical information. http://www.rndsystems.com

34. Wagoner, I.E., Snavely, DoD., Conway, G.a., Hauntz., E.A., Merrill, W.H., Intramyocardial injection of fibroblast growth factor -1 for treatment of refractory angina pectoris, the initial US experience. Circulation. 2004, 110 - 395.

35. Wagoner, LE., Merrill, W., Jacobs, J., Conway, g. Boehmer, J. Thomas, K.Stegmann, T.J. angiogenesis Protein Therapy with Human Fibroblast Growth Factor (FGF-1): Results of A Phase I Open Label, Dose Escalation Study In Subjects with CAD Not Eligible for PC1 or CABG. Circulation 116: 443, 2007.

Proforma

Role of Intravitreal Bevacizumab in the Management of Various Retinal Vascular Diseases

Institute of Ophthalmology, Joseph Eye Hospital, Tiruchirapalli

Name : Age: Sex: S.No

Address : M.R. No.:

Retina No.:

Phone: DOB:

Complaints:

Personal History:

Diabetes : OHA / Insulin / Both / Nil

Hypertension

Dyslipidemia

Cardiac Status

Ocular Examination: RE: LE:

BCVA

IOP

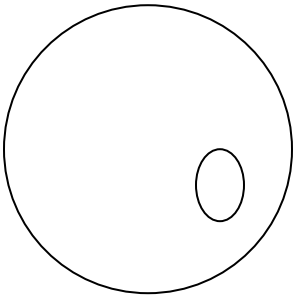
Anterior Segment:

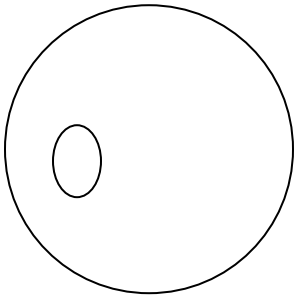
	Cornea	Clear / Hazy	Clear / Hazy
	Iris	NVI + / NVI –	NVI + / NVI –
	Lens	Clear / IMM/ PCL	Clear/IMM/PCL
Posterior Segment			
	PDR	CSME ±	CSME ±
		NVD ±	NVD ±
		NVE ±	NVE ±
		Vit. Hge ±	Vit Hge ±
	BRVO	Mac. Ede. ±	Mac. Ede. ±
		NVD ±	NVD ±
		NVE ±	NVE ±
		Vit. Hge ±	Vit Hge ±
	CRVO	Mac. Ede. ±	Mac. Ede. ±
		NVD ±	NVD ±
		NVE ±	NVE ±
		Vit. Hge ±	Vit Hge ±
	ARMD	Mac. Ede. ±	Mac. Ede. ±
		NVD ±	NVD ±
		NVE ±	NVE ±
		Vit. Hge ±	Vit Hge ±

Provisional Diagnosis:

Fundus Photograph: Date:

FFA: Date: Findings:





OCT: Date:

Macular Thickness

Macular Edema

Details of Intravitreal Bevacizuman (Avastin)

Follow up:

Duration	BCVA	IOP	OCT	Fundus Photograph	FFA	Regression of New vessels NVI / NVD / NVE/ VH
3 days						
2 weeks						
4 weeks						
2nd month						
3rd month						
4th month						
5th month						
6th month						

Master Chart

Click the Link Above

Sno	Name	Age	Sex	Pre Injection				Post injection 3 days		Post injection 2 weeks		Post injection 1 month		Post injection 2 month		Post injection 3 month		Post injection 4 month		Post injection 5 month		Post injection 6 month	
				Retina No	BCVA	BCVA (in Deci)	ProDiag	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)
1	Vijayan	47	M	6146673 2273/07	1/60	0.02	PDR	1/60	0.02	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03
2	Ramadoss	69	M	573932 871/2007	1/60	0.02	PDR	6/18	0.33	6/12	0.50	6/12	0.50	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
3	Janaki Kandasamy	57	F	610326 /07 1057/1999	5/60	0.08	PDR	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17
4	Shakidullah	54	M	621135 2500/ 2007	1/60	0.02	PDR	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02
5	Lakshmiammal	55	F	599656 1753/07	1/60	0.02	PDR	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10
6	Baskar	40	M	597972 1269/07	2/60	0.03	PDR	1/60	0.02	1/60	0.02	6/36	0.17	6/24	0.25	6/24	0.25	6/6	1.00	6/6	1.00	6/6	1.00
7	Dhanalaxmi	59	F	580728 983/07	5/60	0.08	PDR	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25
8	Punithavathy Paramasivam	61	F	574903 39/2005	6/60	0.10	PDR	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
9	Petchiammal	45	F	524645 1744/06	1/60	0.02	PDR	1/60	0.02	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03
10	Chellammal	75	F	597223 1619/07	2/60	0.03	ARMD	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03	2/60	0.03
11	Kalavathy	50	F	516542 1489/06	6/60	0.10	PDR	6/60	0.10	6/36	0.17	6/60	0.10	6/60	0.10	6/60	0.10	6/36	0.17	6/36	0.17	6/36	0.17
12	Antoniyammal	39	F	659277	5/60	0.08	BRVO	6/12	0.50	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
13	Rengarajan	58	M	661902 951/08	6/24	0.25	PDR	5/60	0.08	6/18	0.33	6/60	0.10	6/60	0.10	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
14	Siva Subramaniyan	49	M	644180	6/60	0.10	PDR	5/60	0.08	6/60	0.10	2/60	0.03	2/60	0.03	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
15	Dharmalingam	52	M	635953 3014/07	1/60	0.02	PDR	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33
16	MsHametha	48	F	665218	5/60	0.08	PDR	6/60	0.10	6/18	0.33	6/18	0.33	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
17	Leelavathi	60	F	666335 1137/08	6/60	0.10	ARMD	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17
18	Tamilarasi	55	F	659726 851/08	5/60	0.08	PDR	6/24	0.21	6/24	0.21	6/24	0.21	6/24	0.21	6/24	0.21	6/24	0.21	6/24	0.21	6/24	0.21
19	Mlyyavoo	53	M	543098 2408/06	5/60	0.08	PDR	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25	6/24	0.25
20	Amanullah	58	M	644703 1542/08	3/60	0.05	PDR	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08
21	Nirijah .P	58	F	531815 1989/06	6/60	0.10	CRVO	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10
22	Aysha Beevi	70	F	674684 1488/08	2/60	0.03	CRVO	5/60	0.08	6/60	0.10	6/36	0.17	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08
23	Natrajan	59	M	644634 299/08	5/60	0.08	ARMD	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50
24	Boopathy	48	M	568722 504/07	6/9	0.67	BRVO	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00
25	Kannathal	55	F	643755 257/08	6/24	0.25	PDR	6/24	0.25	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33

26	Salma Beevi	55	F	647733 408/08	5/60	0.08	PDR	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33
Sno	Name	Age	Sex	Pre Injection				Post injection 3 days		Post injection 2 weeks		Post injection 1 month		Post injection 2 month		Post injection 3 month		Post injection 4 month		Post injection 5 month		Post injection 6 month	
				Retina No	BCVA	BCVA (in Deci)	ProDiag	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)	BCVA	BCVA (in Deci)
27	Thangammal	65	F	627699 2713/07	6/12	0.50	BRVO	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50
28	Abdul Alam	67	M	645364 314/2008	1/60	0.02	ARMD	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08	5/60	0.08
29	Amirtham	54	F	604461 1895/07	5/60	0.08	ARMD	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
30	Sundari	40	F	645825 337/2008	6/12	0.50	PDR	6/24	0.25	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
31	Theresa mary	75	F	674185 1466/08	1/60	0.02	ARMD	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
32	Vasuki	52	F	586645	5/60	0.08	PDR	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33
33	Hevani	46	F	665810 1121/08	6/36	0.17	PDR	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17
34	Prema	60	F	674411 1473/08	1/60	0.02	PDR	6/9	0.67	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00
35	Muthusamy	48	M	402645	6/9	0.67	PDR	5/60	0.08	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
36	Raju	59	M	509900 1093/05	4/60	0.07	PDR	5/60	0.08	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17
37	Sugirtha	39	F	679801 1710/08	3/60	0.05	PDR	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
38	Radhakrishnan	70	M	680540 1743/08	4/60	0.07	ARMD	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
39	Thangaraj	56	M	546475 2421/2005	2/60	0.03	PDR	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00	6/6	1.00
40	Govindaraj	54	M	596274 1598/07	2/60	0.03	PDR	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10	6/60	0.10
41	Suppanna	49	M	673652 1709/08	1/60	0.02	PDR	1/60	0.02	1/60	0.02	6/60	0.10	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02
42	Mohanambal	71	F	677870 1631/08	6/60	0.10	ARMD	5/60	0.08	6/36	0.17	6/12	0.50	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17	6/36	0.17
43	Charles	61	M	661567 936/08	6/60	0.10	PDR	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
44	Thomas	62	M	663462 1027/08	6/60	0.10	PDR	1/60	0.02	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33
45	Karuppanna	57	M	412197	5/60	0.08	ARMD	6/18	0.33	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50
46	Dhevamani Pannerselvam	65	F	680921 1763/08	6/60	0.10	ARMD	6/36	0.17	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33	6/18	0.33
47	Lakshmi	60	F	681319 1773/08	1/60	0.02	PDR	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67	6/9	0.67
48	Punitha	58	F	676061 1557 / 08	6/60	0.10	PDR	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50	6/12	0.50
49	Managalambal	66	F	673728 1446/08	1/60	0.02	ARMD	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02	1/60	0.02
50	Anjalai	45	F	681701	1/60	0.02	CRVO	3/60	0.05	3/60	0.05	3/60	0.05	3/60	0.05	3/60	0.05	3/60	0.05	3/60	0.05	3/60	0.05

PDR - Diabetic Retinopathy

BRVO - Retinal Venous Occlusion
CRVO - Central Retinal Vein Occlusion
ARMD - Age Related Macular Degeneration